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Anthropometrically estimated total body water volumes are larger than modeled urea volume in chronic hemodialysis patients: Effects of age, race, and gender

JOHN T. DAUGIRDAS, TOM GREENE, THOMAS A. DEPNER, CAMERON CHUMLEA, MICHAEL J. ROCCO, and GLENN M. CHERTOW, FOR THE HEMODIALYSIS (HEMO) STUDY GROUP

National Institutes of Health, NIDDK, Bethesda, Maryland

Anthropometrically estimated total body water volumes are larger than modeled urea volume in chronic hemodialysis patients: Effects of age, race, and gender.

Background. The modeled volume of urea distribution (Vm) in intermittently hemodialyzed patients is often compared with total body water (TBW) volume predicted from population studies of patient anthropometrics (Vant).

Methods. Using data from the HEMO Study, we compared Vm determined by both blood-side and dialysate-side urea kinetic models with Vant as calculated by the Watson, Hume-Weyers, and Chertow anthropometric equations.

Results. Median levels of dialysate-based Vm and blood-based Vm agreed (43% and 44% of body weight, respectively). These volumes were lower than anthropometric estimates of TBW, which had median values of 52% to 55% of body weight for the three formulas evaluated. The difference between the Watson equation for TBW and modeled urea volume was greater in Caucasians (19%) than in African Americans (13%). Correlations between Vm and Vant determined by each of the three anthropometric estimation equations were similar; but Vant derived from the Watson formula had a slightly higher correlation with Vm. The difference between Vm and the anthropometric formulas was greatest with the Chertow equation, less with the Hume-Weyers formula, and least with the Watson estimate. The age term in the Watson equation for men that adjusts Vant downward with increasing age reduced an age effect on the difference between Vant and Vm in men.

Conclusion. The findings show that kinetically derived values for V from blood-side and dialysate-side modeling are similar, and that these modeled urea volumes are lower by a substantial amount than anthropometric estimates of TBW. The higher values for anthropometry-derived TBW in hemodialyzed patients could be due to measurement errors. However, the possibility exists that TBW space is contracted in patients with end-stage renal disease (ESRD) or that the TBW space and the urea distribution space are not identical.

Key words: total body water volume, hemodialysis, urea.

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Mathematical modeling of urea kinetics during and between intermittent hemodialyses allows calculation of the urea distribution volume. The volume is calculated by computing the amount of urea nitrogen removed during a dialysis treatment and then dividing by the consequent reduction in serum urea nitrogen. For example, if one computes that during a given treatment 21 g of urea nitrogen has been removed, and that the resulting urea reduction due to this treatment is 0.7 g/L, one can infer that the volume of urea distribution is 30 L. The urea distribution volume computed in this fashion is called the modeled volume (Vm) and is commonly expressed as a postdialysis value. Vm can be monitored in a given patient over time to guide changes in the dialysis prescription and to clarify the cause of shortfalls in delivered therapy [1].

Urea is believed to distribute in the total body water [2, 3], which can be estimated from formulas based on various combinations of the patient's height, weight, gender, and age and sometimes other factors. When estimating an initial dialysis prescription for patients, clinicians often compute the initial dose of dialysis using one of these anthropometric formulas (Vant). These prediction equations have been derived by various means. The widely used equation by Watson, Watson, and Blatt [4] was based on a meta-analysis of previous studies where total body water was estimated using a variety of dilution techniques and markers of water volume. The equation derived by Hume and Weyers [5] and Du Bois and Du Bois [6] was derived using tritiated water as a marker. An equation proposed by Chertow et al [7] was based on bioimpedance measurements. Whereas the Watson and Hume-Weyers equations were based on data in non-dialysis subjects, the Chertow equation was derived from a population with end-stage renal disease (ESRD).

Several authors who have examined this issue critically have found that the modeled urea distribution volume in hemodialysis patients is lower than the water volume predicted by anthropometric equations [8–13]. However, a

formal double-pool urea kinetic model was not used in all such studies [8, 9], and in several of these papers, dialysate-side Vm was markedly lower than blood-side Vm. The purpose of the present study was to compare the modeled urea distribution volume with anthropometric estimates of total body water in patients enrolled in the National Institutes of Health (NIH) Hemodialysis (HEMO) Study, applying double-pool modeling concepts in a large number of patients.

METHODS

The NIH HEMO Study

The NIH HEMO Study was a prospective, randomized, multicenter clinical trial designed to study survival, hospitalizations, and a number of secondary end points in patients randomized to different levels of dialysis dose and membrane flux [14]. Using a 2×2 factorial design, half of the qualifying patients were dialyzed with a target equilibrated Kt/V (eKt/V) of 1.45 [20-second postdialysis urea reduction ratio (URR) about 75%] and half were treated with a target eKt/V of 1.05 (20-second postdialysis URR about 67%). In each group, half of the patients were dialyzed using low-flux membranes, and half were dialyzed using high-flux membranes.

Entry criteria for the HEMO Study included a three-dialyses-per-week schedule of dialysis for at least 3 months, aged 18 to 80 years, residual renal clearance <1.5 mL/min per 35 L of urea volume, and anticipated ability to achieve a target eKt/V of 1.45 during a 4½-hour dialysis [14, 15]. Because of this last entry criteria, very large patients were likely excluded from the HEMO Study, although centers had the opportunity to test whether or not a high target eKt/V could be achieved during a baseline, prerandomization phase of the trial.

Baseline period. During this baseline period, two modeling sessions were performed while patients received their prestudy dialysis prescription. This gave baseline adequacy information as well as an initial estimate of each patient's urea distribution volume. The patients were then studied during at least two additional dialysis sessions using one of the approved HEMO Study dialyzers (the clearances of which had been characterized both in vitro and in vivo) in which blood flow rate, dialysate flow rate, and session length had been adjusted to attempt to achieve a target eKt/V of 1.45. If the target eKt/V could not be reliably achieved, patients were not randomized into the follow-up phase of the study.

During the baseline period, modeling depended on a predialysis blood urea nitrogen (BUN) and a 20-second postdialysis BUN only. No delayed postdialysis BUN samples were drawn, and urea removal in the dialysate was not quantified.

Follow-up session (F4) methods. After randomization, half of the patients were maintained on the high-goal prescription with a target eKt/V of 1.45, whereas in the remainder the prescription was set to a target eKt/V of 1.05 (URR about 0.65). During follow-up, patients underwent monthly predialysis and postdialysis BUN determinations that were used to compute single-pool Kt/V (spKt/V) and eKt/V. During month 4 of follow-up (F4), a more intensive modeling session was scheduled for all patients. During this particular session, additional blood samples were drawn 1 hour into dialysis, including dialyzer blood inflow and outflow samples, and a delayed blood sample was taken 30 minutes after dialysis in addition to the usual 20-second postdialysis sample to permit better extrapolation of postdialysis urea rebound.

In a substudy of 146 patients at the F4 session, total urea removed in the spent dialysate was measured with the Baxter Biostat (Baxter Corp., Deerfield, IL, USA) [16]. This device calculates the total amount of urea removed in the spent dialysate from the dialysate flow rate, ultrafiltration rate, session length, and dialysate outflow urea nitrogen concentration measured at 5-minute intervals in the first 30 minutes of dialysis and at 10-minute intervals thereafter. The dialysate urea nitrogen outflow levels combined with the dialysate flow rate were used to compute total urea nitrogen removed in the dialysate.

During the Biostat sessions, samples for BUN were taken predialysis, at 1 hour from the dialyzer blood inlet and outlet lines, and 20 seconds and 30 minutes after the completion of dialysis, allowing computation of equilibrated postdialysis BUN values.

Subjects

Patient data for the present analysis were taken from both modeling sessions performed at baseline (no delayed postdialysis BUN and no dialysate urea values) and from those sessions at F4 where both dialysate and blood-side modeling had been performed. A number of additional inclusion criteria were applied, namely (*1*) dialysis via a peripheral arteriovenous (AV) access, (*2*) access recirculation $<15\%$ by the slow-flow urea method (as per [17], but modified to use a flow reduction to 50 to 80 mL/min for 20 seconds prior to sampling), (*3*) no above-the-knee amputation, (*4*) self-reported race was Caucasian or African American, (*5*) the session was conducted on an "official" HEMO Study–approved dialyzer, (*6*) valid measurements of predialysis and postdialysis BUN with the postdialysis BUN between 10% and 60% of the predialysis BUN, and (*7*) the patient had at least three modeling sessions satisfying conditions 1 to 6.

A total of 5308 modeled dialyses in 1124 randomized patients satisfied these criteria during the baseline period. Means of volumes were calculated after excluding the most deviant volume in cases where the coefficient of variation was greater than 10%. Patients were retained for the F4 study if conditions 1 to 6 described above

were satisfied, the 30-minute postdialysis BUN was obtained, and if no more than two of the individual measurements sampled at 5- to 10-minute intervals by the Biostat device were identified by that device as invalid.

Urea modeling in the HEMO Study

In the HEMO Study, dialysis treatment adequacy was assessed using several blood-side and dialysate-side modeling methods [15]. A relatively small number of dialyzers were used, the urea clearance of which were characterized both during in vitro studies and in vivo by obtaining simultaneous inlet/outlet BUN samples on many occasions. Postdialysis blood samples, routinely obtained 15 to 20 seconds after dialysis, were also drawn 30 minutes after dialysis in a subgroup of patients for dialysate-side urea kinetics [12, 16]. The classic double-pool, variable volume model of urea kinetic during and between dialyses was defined by:

$$d(C_1V_1)/dt = G - K_c(C_1 - C_2) - C_1(K_d + K_r)$$

$$d(C_2)/dt = -K_c(C_2 - C_1)/V_2$$

$$dV_1/dt = -Q_f$$

where C is the concentration of urea, subscript 1 refers to the proximal dialyzed compartment (nominally taken to be the extracellular compartment in classic double-pool modeling) and subscript 2 to the distal equilibrating compartment (nominally taken to be the intracellular compartment in classic double-pool modeling), G is the urea generation rate, K_c is the intercompartment urea mass transfer coefficient, K_d is the dialyzer urea clearance, K_r is the patient's native kidney clearance, and Q_f is the rate of fluid loss during dialysis (negative between dialyses). The volume of the distal equilibrating compartment V_2 is assumed to be constant over time and twice the volume of the proximal compartment at the end of dialysis. Sensitivity analyses showed that the ratio of the volumes of the two compartments [V_2 ranging from 27% to 45% of ($V_1 + V_2$)] had only a trivial effect on calculated modeled volumes with the modeling method used.

Modeled urea volume (Vm_{dp}) from 30-minute post-BUN and blood-side modeling. Vm_{dp} was estimated by numerically curve fitting the above equations for the double-pool model to BUN measurements obtained predialysis, postdialysis (20-second slow-flow method), and 30 minutes postdialysis [15]. Values for Vm and the intercompartment mass transfer coefficient (K_c) were selected that provided maximum agreement between the model BUN predictions and the three measured BUNs. These measurements, which were considered the gold standard (double-pool modeled volume), were done only during the F4 study. Details of the methods used to estimate the in vivo dialyzer clearances used are presented separately [18].

Modeled urea volume ($Vm_{sp\text{-}adj}$) from 20-second post-BUN and blood-side modeling, with appropriate adjustments to approximate a double-pool volume. $Vm_{sp\text{-}adj}$ (single-pool adjusted) was measured using single-pool, blood-side kinetics and was then adjusted to better approximate double-pool modeled volume. Single-pool modeled V (Vm_{sp}) was obtained by applying the two-BUN method of Depner and Cheer [19]. This iterative method initially computes an estimated Vm_{sp} based on anthropometric parameters, and then adjusts the calculated urea generation rate until the estimated predialysis BUN at steady-state equals the actual predialysis BUN. After each iteration, Vm_{sp} is recalculated from standard variable-volume single-pool equations, based on the estimated dialyzer clearance, urea generation rate, ultrafiltration rate, session length, and predialysis and postdialysis BUN values. An estimate of the double-pool V ($Vm_{sp\text{-}adj}$) was then obtained from V_{sp} based on a previously determined estimate of the ratio of single-pool and double-pool V and the fall in BUN during dialysis:

$$Vm_{sp\text{-}adj} = V_{sp} / (\ln [(F \times C_0/C_t)]/[F \times \ln (C_0/C_t)])$$

where C_{eq} is an estimate of the equilibrated postdialysis BUN derived from application of the rate equation, C_0 and C_t denote the predialysis and postdialysis BUN, and $F = C_t / C_{eq}$ [20–22]. Measurements of $Vm_{sp\text{-}adj}$ were made during the baseline as well as the F4 period.

For both of the methods described above for measuring V, dialyzer clearance was calculated using the blood flow adjusted for prepump pressure effects, and the estimated in vivo dialyzer K_0A [18, 23].

Modeled urea volume (Vm_{ddq}) from Biostat dialysate urea values, estimated dialysate volume, and from pre- and 30-minute post-BUN. Vm_{ddq} was calculated during the F4 session using direct dialysate quantification:

$$Vm_{ddq} = (A - G \times T - Q_f \times T \times C_{pre})/(C_{pre} - C_{eq})$$

where A is the total urea removed estimated by the Biostat device, G is the urea generation rate, T the session length, Q_f the ultrafiltrate volume, C_{eq} the equilibrated postdialysis BUN, and C_{pre} the predialysis BUN. For the direct dialysate method, C_{eq} was estimated by applying a numerical curve fit of the predialysis, postdialysis, and 30-minute postdialysis BUN to the double-pool variable volume model, similar to that used to estimate Vm_{dp} above.

The predialysis blood specimen was drawn from the access device before giving saline or heparin. The postdialysis blood samples were drawn 15 to 20 seconds after slowing the blood pump to 50 to 80 mL/min, and the delayed postdialysis samples (F4 session only) were obtained 30 minutes after the end of the dialysis session. During the F4 sessions, even though inlet and outlet BUN samples were obtained during individual sessions, for consistency, the population average in vivo dialyzer mass transfer area coefficient (K_0A) was used instead of a K_0A based on the dialyzer inlet/outlet extraction ratio for each session.

Calculation of anthropometric volumes

Anthropometric formulas estimate the volume of body water (V) from gender, weight, height, age, and diabetic status using the following equations:

Hume-Weyers

Men: V

$$= -14.01 + 0.2968 \times \text{weight} + 0.1948 \times \text{height}$$

Women: V

$$= -35.27 + 0.1838 \times \text{weight} + 0.3445 \times \text{height}$$

Watson

Men: V

$$= 2.447 + 0.3362 \times \text{weight} + 0.1074 \times \text{height} - 0.09516 \times \text{age}$$

Women: V

$$= -2.097 + 0.2466 \times \text{weight} + 0.1069 \times \text{height}$$

where age is in years, height in centimeters, and postdialysis weight in kilograms.

Chertow

$$V = -0.0749\ \text{age} - 1.0178 \times \text{male} + 0.127 \times \text{height} - 0.0401 \times \text{weight} + 0.579 \times \text{diabetes} - 0.000672 \times \text{weight}^2 - 0.0349 \times (\text{age} \times \text{male}) + 0.1126 \times (\text{male} \times \text{weight}) + 0.00104 \times (\text{age} \times \text{weight}) + 0.00186 \times (\text{height} \times \text{weight})$$

where age is in years, height in centimeters, weight refers to the predialysis weight in kilograms, male is equal to 1 for males and 0 for females, and diabetes is 1 for diabetics and 0 for nondiabetics.

Note that the Hume-Weyers approximation for V does not include age. The negative sign for the age term in the Watson equation indicates a decrease in V with age in men, but there is no age term for women. The Chertow equation is designed to compute predialysis V so for the purposes of this study, the weight loss (obtained from the dialysis run sheet) was subtracted from the Chertow V to give a postdialysis value (Adj Chertow).

Statistical analyses

Patient and dialysis characteristics and the volume estimates were summarized for the F4 and the baseline studies by standard descriptive statistics (e.g., mean, median, standard deviation). Volume estimates were compared by presenting the ratio of the mean values of each volume, with standard errors determined by the delta method [24]. These comparisons were provided for all 146 patients combined for the F4 study, but for the baseline data set the sample size (1124) was sufficiently large to provide the volume comparisons in gender and race specific subgroups. For the baseline study the difference between $Vm_{sp\text{-}adj}$ and each of the three anthropometric estimates was related to age by using separate semiparametric multiple regression analyses in males and females to relate the difference between Vant and $Vm_{sp\text{-}adj}$ to a cubic spline function of age while controlling for race and diabetic status. The difference between the anthropometric estimates and $Vm_{sp\text{-}adj}$ was also evaluated by using a multiplicative regression model [25] to relate $Vm_{sp\text{-}adj}$ to a product of Vant with proportional adjustment factors for gender, race, diabetic status, and age. The association of each of the Vant estimates with $Vm_{sp\text{-}adj}$ was evaluated on a patient basis in terms of the Pearson R to evaluate linear association, the concordance R [26] to evaluate the overall level of agreement, incorporating both bias and the degree of linear association, and the median absolute error to evaluate overall agreement. These three statistics were compared between the anthropometric estimates by applying the bootstrap method with 800 bootstrap samples [27] to estimate the standard errors of differences in the statistics between the respective estimates. All reported P values are two-sided, and regarded as statistically significant if $P > 0.05$ without adjustment for multiple comparisons.

Table 1. Patient characteristics for 4-month follow-up study ($N = 146$ patients)

	Mean	Median	SD
Age *years*	57.90	58.97	13.65
Post weight *kg*	71.30	69.50	13.20
Height *cm*	166.65	166.35	8.87
Race (% African American)	61	—	—
Body mass index	25.73	25.25	4.75
Serum creatinine *mg/dL*	10.88	10.60	2.81
Qb *mL/min*	378.35	400.0	68.01
Qd *mL/min*	702.67	800.0	120.70
Td *min*	210.60	210.0	28.61
spKt/V	1.54	1.56	0.23
eKt/V	1.30	1.36	0.21
URR	0.72	0.72	0.05

Abbreviations are: Qb, blood flow rate; Qd, dialysate flow rate; Td, session length; spKt/V, single-pool Kt/V; eKt/V, equilibrated Kt/V (derived from spKt/V and the rate equation); URR, urea reduction ratio.

RESULTS

Follow-up period F4 session results

These results pertain to the modeling sessions performed at F4, 4 months after randomization, where multiple blood samples during and after dialysis were obtained, including a 30-minute postdialysis BUN sample, and where the Biostat was used to measure urea in the spent dialysate.

Patient characteristics. As shown in Table 1, of the 146 patients studied, 39 were Caucasian males, 18 were Caucasian females, 47 were African American males, and 42 were African American females. Other races were excluded from this analysis.

Table 2. Anthropometric and modeled volumes (liters) $N = 146$ patients

	Mean	SD	Median V *L*	Median V/weight *L/kg*	Ratio of mean with respect to Vm_{ddq}	Ratio of mean with respect to $Vm_{sp\text{-}adj}$
Watson V	36.61	5.63	36.84	0.52	1.17	1.16
Hume-Weyers V	37.58	5.79	38.09	0.54	1.20	1.19
Adj Chertow V[a]	37.99	6.36	37.75	0.55	1.22	1.20
Vm_{dp}[b]	32.05	6.26	31.25	0.45	1.03	0.99
$Vm_{sp\text{-}adj}$[c]	31.66	6.25	31.21	0.44	1.01	—
Vm_{ddq} (Biostat)	31.22	8.10	31.81	0.43	—	0.99

[a]The Chertow estimate was adjusted to the postdialysis V
[b]Vm_{dp} includes a blood urea nitrogen (BUN) 30 minutes postdialysis
[c]$Vm_{sp\text{-}adj}$ is the single-pool volume based on a slow-flow 20-second postdialysis BUN and adjusted to approximate the double-pool volume (see **Methods** section)

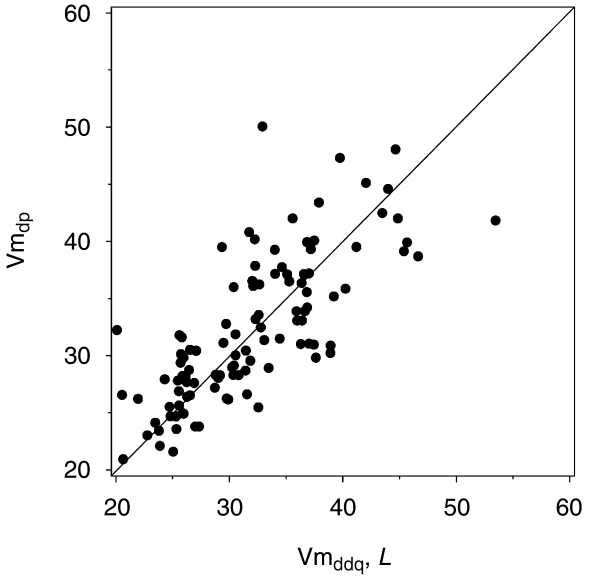

Fig. 1. Agreement between dialysate-side modeled volume urea distribution (Vm_{ddq}) and blood-sided Vm_{dp}. Patients were studied at the F4 session, 4 months into follow-up. The change in urea concentration was calculated using the equilibrated postdialysis blood urea nitrogen (BUN) extrapolated from a 30-minute postdialysis sample for both the blood-side and dialysate-side Vm methods. *R* denotes the Pearson correlation. $N = 146$, $r = 0.62$, median Δ volume = 0.01 L.

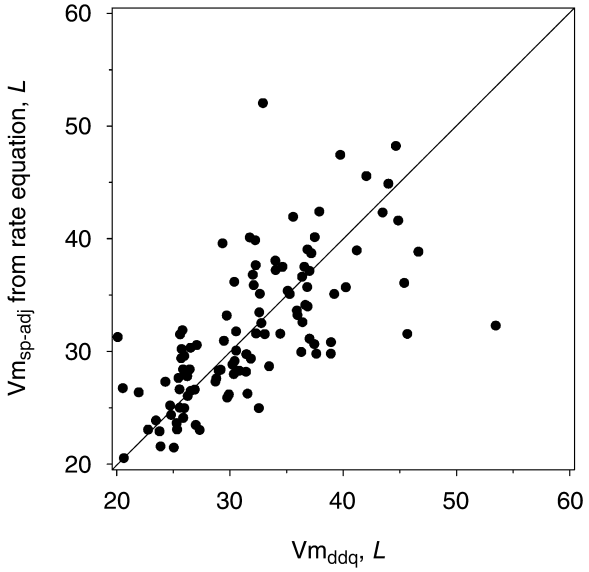

Fig. 2. Agreement between dialysate-side modeled urea distribution (Vm_{ddq}) and blood-sided $Vm_{sp\text{-}adj}$. Patients were studied at the F4 session, 4 months into follow-up. The change in urea concentration was calculated using the equilibrated postdialysis blood urea nitrogen (BUN) extrapolated from a 20-second postdialysis sample for the blood-sided Vm method, and using an equilibrated post-dialysis BUN extrapolated from the 30-minute postdialysis BUN for the dialysate-side Vm method. *R* denotes the Pearson correlation. $N = 146$, $r = 0.58$, median Δ volume = 0.26 L.

Anthropometric TBW vs. modeled urea volumes. Table 2 shows that the three anthropometric estimates of V are similar and there were no statistically significant differences among the three modeled estimates of Vm. The modeled urea volumes had median volume to weight ratios (L/kg × 100%) of 43% to 45%, whereas the median anthropometric TBW volume/weight ratios were 52% to 55%. Accordingly, each of the three modeled urea volume values were substantially and significantly lower than any of the three anthropometric TBW estimates ($P < 0.001$). The ratios (SE) of the respective mean estimates of each Vant to mean Vm_{ddq} were Watson V, 1.17 (0.02); Hume-Weyers V, 1.20 (0.02); Adj Chertow V, 1.22 (0.02); Vm_{dp} 1.03 (0.02); $Vm_{sp\text{-}adj}$ 1.01 (0.02). The ratios with respect to $Vm_{sp\text{-}adj}$ were Watson V, 1.16 (0.01); Hume-Weyers V, 1.19 (0.01); Adj Chertow V, 1.20 (0.02), Vm_{dp} 1.01 (0.02).

Agreement among modeled estimates of urea volume (Vm_{dp}, $Vm_{sp\text{-}adj}$, Vm_{ddq}). In Figures 1 and 2, estimates of urea volume for individual patients computed using blood-side modeling (vertical axis) are compared to the dialysate-side (DDQ) estimates (horizontal axis). For computation of Vm_{dp} shown in Figure 1, the equilibrated postdialysis BUN was extrapolated from the 30-minute postdialysis sample using double-pool modeling. The same value of equilibrated postdialysis BUN was used to compute Vm_{ddq}. In Figure 2, $Vm_{sp\text{-}adj}$ is based on extrapolating the 20-second postdialysis BUN to an equilibrated postdialysis BUN as described in the **Methods** section. Vm_{ddq} values in Figure 2 are identical to the Vm_{ddq} values shown in Figure 1.

Table 3. Patient and treatment characteristics at baseline, by gender and race

	Caucasian males $N = 232$			African American males $N = 316$		
	Mean	Median	SD	Mean	Median	SD
Age *years*	57.76	61.07	15.75	54.53	54.58	13.08
Post weight *kg*	72.20	70.40	14.12	72.73	70.54	13.55
Height *cm*	171.46	172.20	7.38	172.04	171.85	7.50
Body mass index	24.55	23.91	4.43	24.58	24.00	4.40
Serum creatinine *mg/dL*	10.18	10.20	2.57	12.11	11.90	3.23
Qb *mL/min*	400.59	400.00	39.10	421.32	423.38	41.65
Qd *mL/min*	661.89	650.00	120.61	700.55	700.00	102.32
Td *min*	228.35	235.63	21.09	228.39	230.00	20.78
spKt/V	1.62	1.61	0.13	1.59	1.58	0.12
eKt/V	1.39	1.39	0.11	1.37	1.35	0.10
URR	0.73	0.73	0.03	0.73	0.72	0.03
	Caucasian females $N = 167$			African American females $N = 409$		
	Mean	Median	SD	Mean	Median	SD
Age *years*	57.95	61.14	14.57	59.28	61.26	12.59
Post weight *kg*	66.46	63.62	15.67	67.90	67.02	14.48
Height *cm*	159.14	158.70	7.61	160.45	160.00	6.82
Body mass index	26.34	24.88	6.52	26.38	25.98	5.43
Serum creatinine *mg/dL*	8.56	8.40	2.08	10.19	10.10	2.57
Qb *mL/min*	379.21	385.71	50.72	413.51	412.50	41.17
Qd *mL/min*	644.50	600.00	120.28	675.81	650.00	114.28
Td *min*	207.96	210.00	22.11	208.38	210.00	22.16
spKt/V	1.73	1.72	0.17	1.71	1.70	0.16
eKt/V	1.46	1.44	0.15	1.44	1.42	0.14
URR	0.76	0.76	0.03	0.75	0.75	0.03

Abbreviations are: Qb, blood flow rate; Qd, dialysate flow rate; Td, session length; spKt/V, single-pool Kt/V; eKt/V, equilibrated Kt/V (derived from spKt/V and the rate equation); URR, urea reduction ratio.

Baseline period results

For the baseline study a larger sample of 1124 patients was available, and both anthropometric and modeled estimates of V were averaged over at least three kinetic modeling sessions for each patient. However, since dialysate sampling was not done, and only the standard predialysis and postdialysis BUNs were obtained, the modeled V was computed using only the $V_{sp\text{-}adj}$ technique.

Patient characteristics by gender and race. As shown in Table 3, 548 male patients and 576 female patients were analyzed. Among Caucasians, there was a preponderance of males (232) to females (167), whereas this gender ratio was reversed among African Americans with 316 males and 409 females. The mean URR was relatively high (73% to 76%) since several sessions were set to determine whether or not patients could achieve the high-goal dialysis prescription.

Anthropometric TBW vs. modeled urea volumes by gender and race. Table 4 compares the three anthropometric TBW volumes to $Vm_{sp\text{-}adj}$ by gender and race. As expected, all volumes were significantly higher in males compared to females. For example the median Watson volume/weight ratio was 55% or 56% in Caucasian and African American males, respectively, whereas it was only 48% and 47% in Caucasian and African American females. It is clear that in all race and gender subgroups, anthropometric estimates of TBW were markedly higher than the modeled urea volume, where the median volume/weight ratios for urea were 46% and 48% in Caucasian and African American males and 40% and 41% in Caucasian and African American females.

The differences expressed as percents are listed in Table 5. Here we see that the anthropometric equation for TBW with the least difference from the modeled urea volume is the Watson equation, while the Hume-Weyers equation had the second smallest difference. The newer TBW equation by Chertow et al tended to be greater than the modeled V by a slightly greater amount. The differences between modeled urea volume and anthropometric estimates of TBW were significantly greater in males than in females and were also significantly greater in Caucasians than in African Americans.

Effects of age and other factors on differences between anthropometric estimates of TBW and modeled urea distribution volume

The Watson equation has an age-related term for males that reduces the predicted value for Vant with increasing age at a given height and weight. The equation has no such term for females, as in the original Watson meta-analysis, a marked age effect in females was not found. Figures 3 and 4 examine this issue by plotting the difference between Vant − Vm as a function of patient age controlling for diabetic status and race, with Figure 3 showing the results for males and Figure 4 for females.

Table 4. Volume estimates at baseline

	Caucasian males $N = 232$			African American males $N = 316$			All males $N = 548$		
	Mean V (SD)	Median V	Median V/weight	Mean V (SD)	Median V	Median V/weight	Mean V (SD)	Median V	Median V/weight
Watson V *L*	39.63 (5.12)	38.61	0.55	40.17 (4.94)	39.78	0.56	39.94 (5.02)	39.31	0.56
Hume-Weyers V *L*	40.80 (4.89)	40.22	0.57	41.07 (4.72)	40.67	0.57	40.96 (4.79)	40.44	0.57
Chertow V *L*	44.76 (5.89)	43.78	0.63	45.23 (5.83)	44.83	0.63	45.03 (5.86)	44.41	0.63
Adj Chertow V *L*	41.68 (5.58)	40.87	0.58	41.99 (5.51)	41.62	0.58	41.86 (5.53)	41.21	0.58
$Vm_{sp\text{-}adj}$ *L*	33.09 (4.94)	33.03	0.46	34.94 (5.16)	34.52	0.48	34.16 (5.15)	33.85	0.48
	Caucasian females $N = 167$			African American females $N = 409$			All females $N = 576$		
	Mean V (SD)	Median V	Median V/weight	Mean V (SD)	Median V	Median V/weight	Mean V (SD)	Median V	Median V/weight
Watson V *L*	31.30 (4.05)	30.79	0.48	31.81 (3.84)	31.61	0.47	31.66 (3.91)	31.37	0.47
Hume-Weyers V *L*	31.78 (4.14)	31.80	0.49	32.52 (4.02)	32.14	0.48	32.31 (4.07)	32.04	0.49
Chertow V *L*	34.68 (4.18)	34.35	0.54	35.44 (4.19)	35.08	0.53	35.22 (4.20)	34.95	0.53
Adj Chertow V *L*	31.98 (4.01)	31.56	0.49	32.62 (3.99)	32.39	0.49	32.44 (4.01)	32.22	0.49
$Vm_{sp\text{-}adj}$ *L*	26.74 (4.70)	25.85	0.40	28.27 (4.81)	27.82	0.41	27.83 (4.82)	27.34	0.41

Table 5. Percent differences between anthropometric estimates and modeled V ($Vm_{sp\text{-}adj}$) at baseline[a]

Anthropometric V measure	Caucasian males ($N = 232$)	Caucasian females ($N = 167$)	African American males ($N = 316$)	African American females ($N = 409$)	All patients ($N = 1124$)
Watson V	19.8 ± 0.9	17.1 ± 1.2	15.0 ± 0.6	12.5 ± 0.7	15.5 ± 0.4
Hume-Weyers V	23.3 ± 0.9	18.8 ± 1.3	17.5 ± 0.7	15.0 ± 0.7	18.1 ± 0.4
Adj Chertow V	26.0 ± 1.0	19.6 ± 1.3	20.1 ± 0.7	15.4 ± 0.7	19.8 ± 0.4

[a]Percent differences in means ± SE. All percent differences significantly greater than 0 ($P < 0.001$).

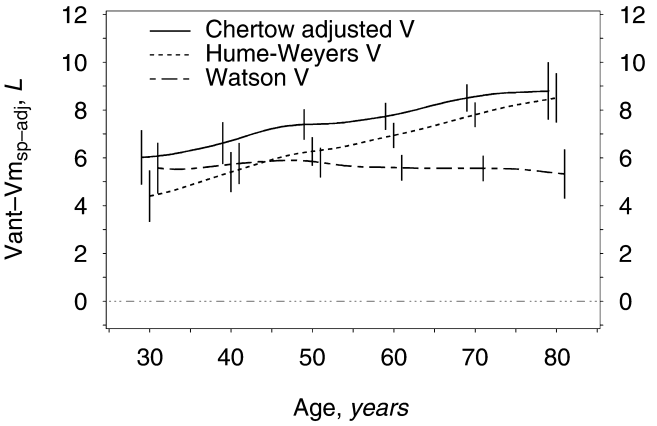

Fig. 3. The effect of age on the difference between each of three measures of anthropometric volume (Vant) and modeled urea volume ($Vm_{sp\text{-}adj}$) in men.

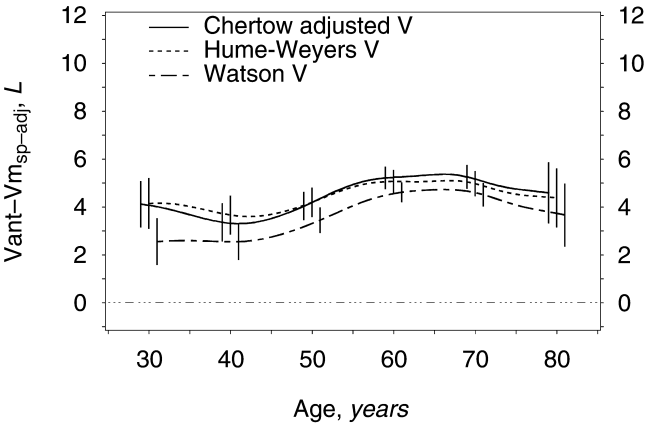

Fig. 4. The effect of age on the difference between each of three measures of anthropometric volume (Vant) and modeled urea volume ($Vm_{sp\text{-}adj}$) in women.

Inspection of Figure 3 shows that the differences between Vant − Vm is similar for the Watson equation for males across age, although it does increase slightly with age. This suggests that the age term in the Watson equation has the benefit of making more constant the difference between its predicted volume and modeled urea volume across age. With the other anthropometric estimates of TBW, the difference between Vant and Vm tends to increase with age, especially in men.

In Figure 4, the difference between anthropometric estimates of TBW and modeled urea volume increases to a lesser extent with age in females. This suggests that the performance of the Watson equation V is only slightly reduced by its lack of an age term for females.

Table 6 shows how the three anthropometric measures of total body water (Watson, Hume-Weyers, adjusted Chertow) relate to the modeled urea volume (as $Vm_{sp\text{-}adj}$) and how this relationship is affected by diabetes, age, gender, and race.

Table 6. Multiplicative regressions of $Vm_{sp\text{-}adj}$ vs. Vant at baseline

Factor	Estimate of Vant		
	Watson	Hume-Weyers	Adjusted Chertow
Overall multiple of Vant (A_{ESRD})	0.824 (0.006)[a]	0.815 (0.006)[a]	0.796 (0.005)[a]
Adjustment for diabetes (A_{diab})	1.033 (0.007)[a]	1.039 (0.007)[a]	1.023 (0.007)[b]
Age adjustment per 10 years in men ($A_{age.m}$)	0.998 (0.004)	0.977 (0.003)[a]	0.982 (0.003)[a]
Age adjustment per 10 years in women ($A_{age.f}$)	0.985 (0.004)[a]	0.992 (0.004)[b]	0.988 (0.004)[b]
Adjustment for female gender (A_{female})	1.033 (0.008)[a]	1.014 (0.008)	1.045 (0.008)[a]
Adjustment for African American race ($A_{Af\text{-}Am}$)	1.043 (0.007)[a]	1.039 (0.008)[a]	1.041 (0.008)[a]
RMSE (L)	3.47	3.56	3.56

Shown are coefficients (SE) for regression models of the form: Vm = Vant × A_{ESRD} × [A_{diab} × if diabetic] × [$A_{age.m}$ × (Age − 50) if male] × [$A_{age.f}$ × (Age − 50) if female] × [A_{female} if female] × [$A_{Af\text{-}Am}$ if African American]. RMSE (root mean square error) estimates the standard deviation of the errors of the regression models in predicting Vm.

[a] Different than 1, $P < 0.001$; [b] different than 1, $P < 0.05$

The first term, $A_{ESRD,}$ indicates the multiplier of Vant necessary to estimate the mean Vm for nondiabetic Caucasian males of age 50 years, and the remaining terms indicate proportional adjustments for gender, African American race, diabetes, and age. These proportionality constants can be used to construct a prediction equation based on the HEMO Study data for the urea distribution volume starting with any of the well-accepted anthropometric total body water volumes. RMSE is the square root of the mean squared error and is a measure of the overall fit of each anthropometric volume to the modeled urea volume (Vm).

The A_{ESRD} terms, listed in the top row, are less than 1.0 for each of the anthropometric volumes tested. The second row is a term for diabetes and indicates that the urea volume is about 2% to 4% higher in diabetics relative to the anthropometric body water predictions. The next two rows depict age adjustments. Some of the TBW equations have an age term, others do not. The adjustment factors shown suggest that urea volume declines with age, and that this adjustment is made by some of the TBW equations (e.g., Watson) better than others, and also, that this age adjustment is gender-dependent. The additional rows suggest added terms for gender and race to improve the prediction of Vm from each of the anthropometric equations. As can be seen from the last row, which shows the root mean squared error, overall, the Watson equation gave the closest agreement with the modeled urea volume.

These proportionality terms can be used to obtain a new prediction equation for Vm based on anthropometric TBW equations. For example, we can use the Watson equation as a starting point and then the full model from Table 6 for estimating $Vm_{sp\text{-}adj}$ from the Watson TBW volume is:

$$\begin{aligned} Vm = {} & [\text{Watson V}] \times [0.824] \times [1.033 \text{ if diabetic}] \\ & \times [0.998 \times (\text{age} - 50) \text{ if male}] \\ & \times [0.985 \times (\text{age} - 50) \text{ if female}] \\ & \times [1.033 \text{ if female}] \\ & \times [1.043 \text{ if African American}] \end{aligned}$$

If the gender and age terms are omitted from the model, the regression equation estimating $Vm_{sp\text{-}adj}$ from the Watson V is:

$$\begin{aligned} Vm = {} & [\text{Watson V}] \times [0.828] \\ & \times [1.045 \text{ if African American}] \\ & \times [1.032 \text{ if diabetic}] \end{aligned}$$

The RMSE for this simpler model is 3.50, which is only slightly higher than the RMSE of 3.47 for the complete model shown in Table 6.

Table 7. Agreement of anthropometric estimates of V with $Vm_{sp\text{-}adj}$ at baseline

	Pearson *R*	Concordance *R*	Median absolute % error vs. Vm
All patients			
Watson V	0.799	0.606	16.5%
Chertow V	0.786[a]	0.531[a]	20.9%[a]
Hume-Weyers V	0.779[a]	0.544[a]	18.7%[a]
Males			
Watson V	0.711	0.431	17.2%
Chertow V	0.699	0.342[a]	20.0%[a]
Hume-Weyers V	0.685[a]	0.353[a]	22.6%[a]
Females			
Watson V	0.695	0.492	15.9%
Chertow V	0.671[a]	0.428[a]	18.9%[a]
Hume-Weyers V	0.651[a]	0.427[a]	17.8%[a]

[a] Agreement of indicated anthropometric formula with $Vm_{sp\text{-}adj}$ was significantly ($P < 0.05$) poorer than the agreement of Watson V with $Vm_{sp\text{-}adj}$

Association of anthropometric estimates of TBW with modeled urea V on a patient basis

Table 7 summarizes the association of the anthropometric estimates of TBW with $Vm_{sp\text{-}adj}$ on a patient basis for the baseline study. The Pearson *R* values summarize the strength of the linear association of the estimates independently of the systematic underestimation of

$Vm_{sp\text{-}adj}$ by the anthropometric estimates, the concordance *R* incorporates both bias and the strength of linear association, and the median absolute percent error is a measure of the overall agreement. The results suggest that, overall, the Watson equation had a slightly smaller divergence from modeled $Vm_{sp\text{-}adj}$ than the other two equations.

DISCUSSION

Our results showed that modeled urea V was substantially lower than total body water predicted by each of three equations based on anthropometric measurements. We found that the median volume to weight ratios (liter per kilogram, as percent) for modeled urea volume were 48% and 41% for men and women, respectively, whereas Watson volume to weight ratios were 56% and 47%, similar to previously published data. In this respect, our findings confirm those of Pastan and Gassensmith [8], reported in 1992 in a much smaller sample of patients. Other investigators who have examined the issue closely have also found urea distribution volume to be lower than anthropometric total body water estimates [8–13], although the shortfall was not always of the magnitude found in the present study.

Despite the contention that urea distribution volume is equal to TBW, there are few papers in the literature where urea distribution space has been measured using isotopes, and almost none where measurements using both urea and water isotopes have been made in the same patients. In an early paper from 1953, using ^{15}N-labeled urea, San Pietro and Rittenberg [2] measured the urea volume and found a volume to weight ratio of 48% to 50% in three nondialysis subjects. They also measured volume with both ^{15}N-labeled urea and deuterium oxide in a female patient and found that the urea volume was similar to water volume, albeit 5% lower. Pearson et al [28] injected doubly labeled (^{15}N and ^{13}C) urea to six ESRD patients and five control subjects. They found mean urea volume/weight ratios of 50% in the ESRD patients (five females and one male) and 58% in the nondialysis controls (three females and one male). Kloppenburg et al [3], in a methods paper, gave ^{13}C urea to one nondialysis volunteer and one ESRD patient, genders of both unspecified. In the ESRD patient, the urea volume/weight ratio was 52%, whereas in the nondialysis patient the mean urea volume/weight ratio was 62%. The same group then went on to study a larger number of patients, and obtained both DDQ-modeled urea volumes and, in a subset of patients, ^{13}C urea volumes [9]. The volume/weight ratios of their DDQ-modeled urea volumes (44% and 38% for males and females, respectively) were somewhat smaller than our values of 48% and 41%. In a subset of male patients with both DDQ and ^{13}C urea volumes, the volume/weight ratios were 48% for DDQ and 52% for ^{13}C urea. Thus, our results are not inconsistent with previous investigators who have measured urea space in ESRD patients using isotopes or mathematic modeling.

The apparently lower urea distribution volume found in our study might have resulted from underestimation of the amount of urea removed. In the blood-side modeling method, we employed a blood flow correction algorithm that down-regulated the estimated blood flow rate from the nominal flow rate derived from the blood pump rotational speed. At nominal blood flow rates of 200, 300, 400, and 500 mL/min, our algorithm predicted mean delivered blood flow rates of 200, 296, 375, and 418 mL/min, respectively. The derivation and rationale for this blood flow adjustment algorithm are discussed in a separate paper [18]. These adjustments are consistent with several previous studies that demonstrate significant overestimation of flow at high blood flow rates by the rotational speed meters found in all dialysis roller pumps [18, 23]. For the blood tubing used by most of the HEMO Study centers, we found a similar error but of lower magnitude when flows were measured in vitro with warmed saline (unpublished data). In a sensitivity analysis, when we used the lesser corrections determined by the in vitro saline studies (a lowest case scenario), we found that the percent difference between mean Watson V and Vm was 12.4%, which is similar to the 15.5% reported in Table 5.

The agreement in the average amount of urea removed between our double-pool blood-side modeling analysis and dialysate recovery methods in the substudy at 4 months follow-up suggests that a substantial underestimation of urea removed was unlikely, although the possibility remains that urea removal was underestimated by both blood- and dialysate-side modeling methods.

Overestimation of the change in patient urea concentration during dialysis is another potential source of error. Although the amount of urea removed in our patients was computed using different methods, the same reduction in urea concentration was used for each method. If the extrapolated postdialysis BUN was underestimated, then the change in concentration would be overestimated, resulting in an inappropriately low Vm. In a separate HEMO substudy, we compared our extrapolation methods for equilibrated postdialysis BUN from 20-second and 30-minute postdialysis samples with a sample obtained 60 minutes postdialysis and found excellent agreement (HEMO Study Investigators, unpublished results). Furthermore, no investigator has found a large rebound in urea concentration occurring beyond 60 minutes postdialysis [11, 13]. For these reasons, we believe that underestimation of the equilibrated postdialysis BUN leading to underestimation of Vm is unlikely. Recently, in an American Society of Nephrology abstract presented at the 2001 Annual Meeting of the American

Society of Nephrology (abstract #A2367; Jorden M et al, Nephrology; Pediatrics, University Hospital Groningen, The Netherlands) the Groningen group did report apparent excretion of urea into the gastrointestinal tract in dialysis patients. If a gastrointestinal repository of urea does exist in dialysis patients, and if it is relatively resistant to extraction during relatively short-session hemodialysis, but less resistant to equilibration with isotope-labeled water, then this might account for some of the discrepancy between modeled urea volumes found in our study with TBW estimates.

Another factor that might lead to differences between anthropometric TBW estimates and modeled urea volumes in our study would be a difference in body composition between patients with normal renal function and dialysis patients. Two of the prediction equations (Watson and Hume-Weyers) were derived from data in nondialysis individuals, so it could be argued that uremia-mediated effects on body composition caused the true TBW to be reduced in such patients, and that the difference between estimated TBW and modeled urea volume in our study is more apparent than real. The impedance data of Cha et al [29] argue against this premise. The Chertow formula was derived from measurements of body impedance in dialysis patients and was calibrated against deuterium oxide dilution. The Chertow prediction equation for TBW in our patients (corrected to the postdialysis condition) gave results that were quite similar to TBW predicted by either the Watson and Hume-Weyers equations, and these values were still substantially higher than the modeled urea volumes found.

It is unclear whether modeled urea volume in our patients was simply underestimated, or whether there may be a true difference between TBW and urea distribution volumes. Others who also have found urea distribution volume to be lower than TBW estimates have argued that there may be errors in the isotopic determination of TBW from which some of these anthropometric estimating equations were derived. For example, with any water-soluble isotope, if one fails to correct the isotope concentration in the dilution sample for plasma water, this will lead to an approximately 7% overestimation of TBW [9] since only 93% of plasma, on average, is water. Another potential source of overestimation of TBW by deuterium or tritium is proton-proton exchange with nonwater hydrogen-containing molecules in the body. It is not clear to what extent these errors may have been present in the "calibration" of currently used TBW estimating equations. The Watson prediction equations were derived from a meta-analysis of previous papers [4], each of which measured TBW by several different methods. The Hume-Weyers equations are based on measurements using tritiated water [5]. In neither one of these papers is there mention of making a blood water correction. Cha et al calibrated their bioimpedance measurements against deuterated water [29], and apparently the plasma water correction was made in their paper, and the issue of hydrogen self-exchange was recognized and corrected.

Our data also shed light on the need for and appropriateness of gender- and age-related correction factors for some of the anthropometric estimating equations. Our results suggest that, in males, modeled urea distribution volume Vm declines with age, as predicted by the Watson equations, but that Vm also declines with age in females, albeit to a lesser extent. Body composition is known to change with age, with a reduction in muscle mass and increase in fat mass. Given the greater muscularity of young males, this age effect should be more easily measured in males. Our results also suggest that the Watson equations give the closest approximation to Vm in the present dialysis population, and that the age term in the Watson equation properly corrects for age-related bias. Although the Chertow equation also contains age-related terms, it did not correct for the age-effect in males as well as the Watson equation.

Our data further highlight the need for correcting anthropometric prediction equations based on race and, perhaps, diabetes. It is now well known that African American patients tend to have a higher rate of creatinine excretion relative to Caucasians after controlling for age, weight, and height [30]. The difference appears to be a racial effect favoring higher muscle mass in African American patients [31]. A relatively higher muscle mass would, of course, also be reflected in a greater ratio of TBW to weight/height/age for African Americans. Hence, our results suggesting that the difference between anthropometric equations and modeled urea volumes is less in African Americans than in Caucasians is not surprising. Reinterpreted, these results suggest that, for a given age, height, and weight, African Americans have a higher true urea V (Vm) than their Caucasian counterparts. Recently Chumlea et al [32] have found similar results for TBW using deuterated or tritiated water measurements in a nondialysis population. The race bias appeared to be slightly higher in males than in females. These findings suggest that any prediction equation for urea V in dialysis patients should incorporate a correction for race. We also found a small correction factor for diabetes, suggesting that the presence of diabetes results in a 3% to 4% increase in modeled V. The need for a correction factor for diabetes was recognized by Chertow et al, although the magnitude of our correction factor was somewhat larger. Why diabetics might have higher TBW values and even higher urea volumes than predicted is unknown. One hypothesis might relate to cardiovascular disease and autonomic neuropathy, resulting in difficulties in achieving so-called dry weight.

In the past, overestimation of Vm has not invalidated the dialysis prescription, since dialyzer urea clearance

based on in vitro estimates is routinely overestimated [8]. Hence, prescribing the amount of dialysis based on in vitro dialyzer urea clearance and anthropometrically estimated V remains a sound practice. However, when dialyzer clearance is more precisely measured, and when the appropriate double-pool corrections are applied, our data suggest that a substantial difference between modeled urea Vm and anthropometrically derived TBW that is race and gender dependent, is to be expected. If the in vivo dialyzer urea clearance is known or derived from the dialysis machine, it might be better to modify the Watson V or whatever anthropometric equation is used according to the appropriate prediction equations in Table 6 to give a more reliable initial estimate of the urea distribution volume (although the exclusion of very large patients from the HEMO Study by design should be kept in mind).

CONCLUSION

Our results provide further evidence that commonly used equations to predict the TBW markedly overestimate the urea distribution volume in dialysis patients. To what extent this represents (*1*) a true difference between the urea distribution space vs. TBW in dialysis patients, (*2*) a measurement error in modeled urea volume, possibly due to gastrointestinal urea sequestration, (*3*) a measurement error in TBW determined by indicator dilution using deuterium, tritium, or other isotopes in the studies from which common estimating equations were derived, or (*4*) an alteration in body composition in patients with ESRD must remain the object of future studies.

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Reprint requests to John T. Daugirdas, M.D., 15W560 89th Street, Burr Ridge, IL 60527.
E-mail: jtdaugir@uic.edu

APPENDIX: ESTIMATION OF IN VIVO DIALYZER CLEARANCES

In vivo dialyzer clearances used in this study were calculated as follows. First, the in vivo K_oA was estimated using the equation:

$$K_0A = \beta_{KoA} \times [1 + \beta_{Qd} \times (Qd - 500)/300 + \beta_{reuse} \times (\text{reuse number})] \quad \text{(Eq. 1)}$$

where β_{KoA} represents the in vivo K_0A of the dialyzer model at first use with Qd = 500 mL/min, β_{Qd} characterizes the effect of increasing Qd from 500 to 800 mL/min on the in vivo K_0A [8], and β_{reuse} characterizes the effect of the number of reuses under the assumption that the effect of reuse on the in vivo KoA is proportional to the number of reuses within the observed range of Qd. The true Qb was estimated by the formula

$$Qb = Qb_n - \alpha_A \times Qb_n \times ((Qb_n - 200)/100)^{\alpha B} \quad \text{(Eq. 2)}$$

where Qb_n denotes the nominal blood flow from the pump speed. The values of the β_{KoA}, β_{Qd}, β_{reuse}, α_A, and α_B in Eq. 1 and Eq. 2 were obtained by fitting a nonlinear regression model to the observed extraction ratios (defined as $(C_{in} - C_{out})/C_{in}$, where C_{in} and C_{out} represent the inlet and outlet BUN concentrations at full blood flow 1 hour into dialysis) for 1208 patients on arteriovenous accesses. The estimates were as follows:

Parameter	Estimate
β_{KoA}	
Fresenius F8	625
Fresenius F80	651
Baxter CT-190G	751
Baxter CA-210	682
Baxter CA-170	498
Fresenius F50	426
Primus 2000	583
Fresenius F6	489
α_A	0.0122
α_B	2.37
β_{Qd}	0.0549
β_{reuse}	−0.0063

Given (Eq. 1) and (Eq. 2) with the values of the parameters in the above table, the dialyzer clearance Kd was determined at each of the kinetic modeling sessions considered in this report by the formula:

$$Kd = 0.894 \times \left(Qb \times \frac{e^{\frac{K_0A}{Q_b}\left(1-\frac{Q_b}{Q_d}\right)} - 1}{e^{\frac{K_0A}{Q_b}\left(1-\frac{Q_b}{Q_d}\right)} - \frac{Q_b}{Q_d}} \right) \times (1 - Qf/(0.894 \times Qb) + Qf$$

where Qf denotes the ultrafiltration rate.

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